MINI-SYMPOSIUM

Rate control in the medical management of atrial fibrillation

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Two main strategies are available for management of atrial fibrillation: rate control and rhythm control.

The aims of heart rate control in atrial fibrillation are to minimise symptoms associated with excessive heart rates and to prevent tachycardia-associated cardiomyopathy.[1] Rate control involves the use of negatively chronotropic drugs or electrophysiological/surgical interventions to reduce the rapid ventricular rate often found in patients with atrial fibrillation.[2] Although the atria continue to fibrillate, this strategy is considered an effective treatment as it can improve symptoms and reduce the risk of associated morbidity. However, the risk of stroke and occurrence of thromboembolic events occurring is reduced by giving antithrombotic drugs.

Rhythm control involves the use of electrical or pharmacological cardioversion or electrophysiological/surgical interventions to convert the arrhythmia associated with atrial fibrillation to normal sinus rhythm. Patients who have been successfully cardioverted are generally given antiarrhythmic drugs for the long term to help prevent the recurrence of atrial fibrillation. Rhythm control strategies also require the appropriate antithrombotic treatment to reduce the risk of stroke and thromboembolism.

WHAT CONSTITUTES ADEQUATE RATE CONTROL?

The optimal heart rate in atrial fibrillation is not known. Current guidelines define adequate rate control in atrial fibrillation as maintenance of the ventricular rate response between 60 and 80 beats/min at rest and between 90 and 115 beats/min during moderate exercise.[3] A consensus statement has suggested a target heart rate of <90 at rest and <180 bpm during exercise in patients with atrial fibrillation.[4] However, no controlled clinical trials have validated these target rates for preventing all-cause cardiovascular morbidity or mortality, and such recommendations may be flawed. Few data exist that define the most robust method for the assessment of rate control.

Adequate rate control may encompass more than the prevention of fast ventricular rates. However, few systematic studies have explored the effect of rate-slowing drugs on chronotropic competence in atrial fibrillation. The effect of rate regularisation is rarely acknowledged in practice, despite evidence that the mere presence of irregular R–R intervals may also contribute to impairment of ventricular haemodynamic function irrespective of heart rate.[5] Furthermore, atrial contraction contributes between 20% and 40% of the total stroke volume. A marked decrease in cardiac output may occur in atrial fibrillation with the loss of atrial contraction, especially in (mostly elderly) patients with impaired diastolic filling, hypertension and left ventricular hypertrophy.

Although rapid ventricular rates in atrial fibrillation can be detrimental, they should not be too slow either. The heart rate in atrial fibrillation should probably be faster than that in sinus rhythm to maintain an equivalent cardiac output.[6]

Rate-control treatment in atrial fibrillation is based mainly on pharmacological depression of conduction through the auriculoventricular node, except in the case of Wolff–Parkinson–White syndrome, where an agent that increases the refractoriness of accessory pathway tissue (eg, flecainide) is needed. Urgent rate control may require the administration of intravenous β-blockers (eg, esmolol) or non-dihydropyridine calcium antagonists. Adequate ventricular rate control at rest does not always translate into effective control during activity, especially with digoxin monotherapy.[7 8] During exercise, vagal tone (and thus the effect of digoxin) is lost; auriculoventricular conduction is further enhanced by the increased sympathetic tone and is different from that in sinus rhythm.[9] Digoxin is therefore unsuitable for rate-control monotherapy, except in sedentary peoples.

β-Blockers and rate-limiting calcium antagonists are often effective as initial monotherapy for rate control, but a combination of drugs is often necessary to achieve adequate rate control.[10–12] In clinical practice, β-blockers are commonly used with digoxin for control of exercise-induced increased heart rate, but the evidence for the effectiveness of such combination treatment was less good[8 13] compared with that available for combination treatment with a rate-limiting calcium antagonist and digoxin.[8 14 15] Table 1 and fig 1 show the recommendations for rate control.

Although serious adverse effects from rate-control drugs are uncommon, the strategy is not without its limitations and drawbacks. Rate control amounts to negative chronotropic treatment, and may result in slow ventricular rates, sinus bradycardia or heart block (in cases of paroxysmal atrial fibrillation). In some patients, particularly elderly patients, symptomatic bradycardia may require permanent pacing. Of particular importance is that the outcome does not seem to be affected by the achieved heart rates.[16]

In patients who fail to respond to medical means of rate control, non-pharmacological measures such as atrioventricular nodal ablation can be considered.[17] Notably, non-pharmacological treatments of rate control were not widely used in the major rate-control versus rhythm-control studies; only 1–2% of

Table 1 Recommendations for rate control

In patients with permanent atrial fibrillation, who need treatment for rate control:
- β-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in all patients
- digoxin should only be considered as monotherapy in predominantly sedentary patients

In patients with permanent atrial fibrillation, where monotherapy is inadequate:
- to control the heart rate only during normal activities, β-blockers or rate-limiting calcium antagonists should be given with digoxin
- to control the heart rate during both normal activities and exercise, rate-limiting calcium antagonists should be given with digoxin

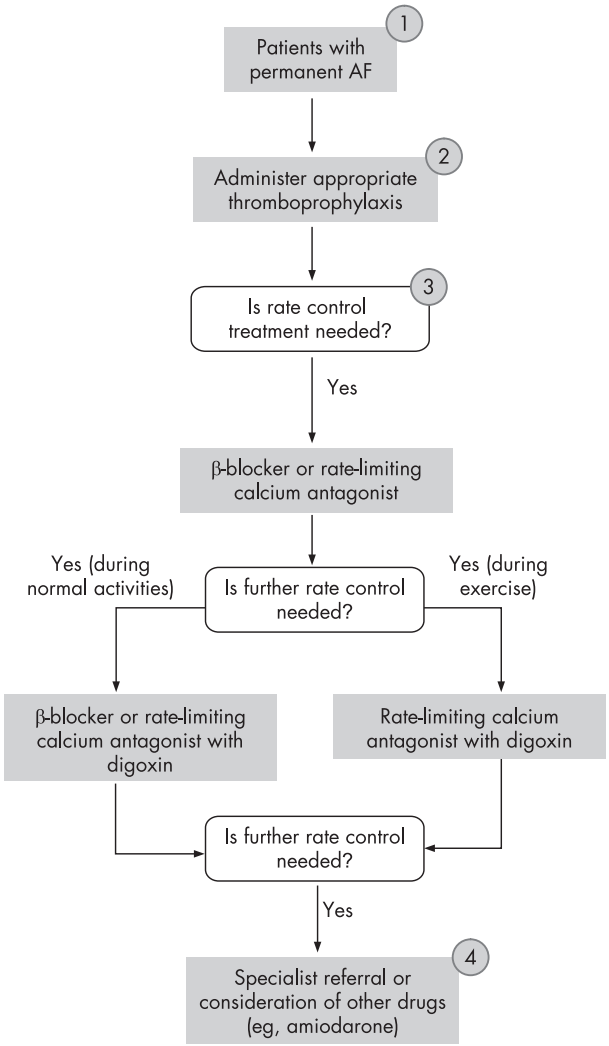

Figure 1 Rate-control treatment algorithm for permanent (and some cases of persistent) atrial fibrillation (AF). (1) Patients with permanent AF include those with persistent AF who have been selected for a rate-control treatment strategy. (2) Based on stroke risk stratification algorithm. (3) Target a resting heart rate of <90 bpm (110 bpm for those with recent-onset AF). Target an exercise heart rate of <110 bpm (inactive), 200 minus age (active). (4) Referral for further specialist investigation should be considered especially in those with lone AF or electrocardiogram evidence of an underlying electrophysiological disorder (eg, Wolffe–Parkinson–White syndrome) or where pharmacological treatment has failed.

patients assigned to rate control had ablation of the auriculo-ventricular node, usually in patients with disturbing symptoms poorly controlled by rate-slowing drugs.

RATE CONTROL VERSUS RHYTHM CONTROL

Until recently, there were uncertainties about the most appropriate initial treatment strategy—either rate control or rhythm control—for individual patients.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study[18] enrolled 4060 patients with atrial fibrillation over 6 years. Patients were aged at least 65 years or had another risk factor for stroke or death. Virtually any atrial fibrillation was allowed, including first-onset atrial fibrillation and paroxysmal atrial fibrillation with a documented paroxysm of at least 6 h duration. The mean follow-up was 3.5 years, with no noticeable mortality difference with either a rate-control or a rhythm-control strategy. Notably, non-cardiovascular deaths (including cancer) accounted for most of the excess deaths in the rhythm-control limb. The rhythm-control strategy was associated with a slightly higher incidence of stroke (7.3% *v* 5.7%), probably owing to more frequent discontinuation of anticoagulant treatment, and greater rates of torsade de pointes (0.8% *v* 0.2%) and hospitalisations (80% *v* 73%). The subgroup analyses suggested a better outcome in younger people <65 years (24%) and in patients with left ventricular dysfunction (23%) who were assigned to rhythm control.

The RAte Control versus Electrical cardioversion (RACE) trial[19] and two pilot studies, Strategies of Treatment of Atrial Fibrillation (STAF)[20] and Pharmacological Intervention in Atrial Fibrillation (PIAF),[21] focused on patients exclusively with persistent atrial fibrillation and pursued an aggressive rhythm-control strategy by means of serial cardioversions and antiarrhythmic drug treatment. The RACE study reported a non-significant trend towards more end points in the rhythm-control arm (22.6% *v* 17.2%), with patients with hypertension (approximately half the total study population) assigned to rhythm control having a markedly higher event rate compared with their counterparts in the rate-control arm (30.8% *v* 17.3%); this relationship was reversed in participants with normotension (12.5% *v* 17.1%). There was no difference in the occurrence of the combined primary end point between rate-control and rhythm-control arms (5.5% *v* 6.1% per year) in the STAF study of 200 patients at high risk.[20] In the PIAF study, the rhythm-control strategy resulted in better exercise performance but did not affect symptoms or quality of life, and was associated with an increased number of hospitalisations for repeat cardioversion and the adverse effects of antiarrhythmic drugs.[21] The HOw to Treat Chronic Atrial Fibrillation (HOT CAFÉ) study enrolled 205 patients with persistent atrial fibrillation.[22] During a mean follow-up of 1.7 years, no difference in the primary end point was seen. However, there was a greater incidence of hospitalisations in the rhythm-control arm
(1 per patient) compared with 0.05 per patient in the rate-control arm, but 88% of admissions were for repeat cardioversion. Finally, the Control of Rate versus Rhythm in Rheumatic Atrial Fibrillation Trial (CRRAFT) in young people (mean age 39 years) who underwent surgery for mitral stenosis[23] reported an advantage of rhythm control with amiodarone over rate control with regard to exercise tolerance and quality of life, although there was no difference in hospitalisation rates, bleeding and thromboembolic events during a follow-up of 1 year.

Overview of the studies

No study found rate control to be inferior to rhythm control or vice versa for the outcome measures of mortality[18–22] or quality of life.[24–27] However, the AFFIRM study[18] found mortality to be higher for rhythm control in patients with coronary heart disease, those without heart failure and those >65 years old. The same study did not find rhythm control to be associated with lower mortality in those with heart failure. Rates of hospitalisation, as well as rates of adverse events, were higher among participants treated according to rhythm-control plans.[18 20 22] The results were generally consistent across studies and considered both older participants with increased risk of stroke[18 19] and younger participants.[21 22]

It was thought that many of the stroke and thromboembolic events in the rhythm-control arm were related to the lack of appropriate use of antithrombotic treatment. Rates of anticoagulation were often not controlled between the two treatment arms in many of the studies. For example, in the AFFIRM study,[18] although anticoagulation was mandatory in the rate-control treatment arm, the decision to continue anticoagulation in the rhythm-control arm after 4 weeks of cardioversion was

Table 2 Non-pharmacological approaches to rhythm control

As some patients with persistent atrial fibrillation will satisfy criteria for either an initial rate-control or a rhythm-control strategy (eg, age >65 years but also symptomatic):
- the indications for each option should not be regarded as mutually exclusive and the potential advantages and disadvantages of each strategy should be explained to patients before agreeing on which to adopt
- any comorbidities that might indicate one approach rather than the other should be taken into account
- irrespective of whether a rate-control or a rhythm-control strategy is adopted in patients with persistent atrial fibrillation, the appropriate antithrombotic treatment should be used

A rate-control strategy should be the preferred initial option in patients with the following conditions with persistent atrial fibrillation:
- age >65 years
- coronary artery disease
- contraindications to antiarrhythmic drugs
- unsuitable for cardioversion
- without congestive heart failure

A rhythm-control strategy should be the preferred initial option in patients with the following conditions with persistent atrial fibrillation:
- those who are symptomatic
- younger patients
- presenting for the first time with lone atrial fibrillation
- those with atrial fibrillation secondary to a treated or corrected precipitant
- those with congestive heart failure

Patients unsuitable for cardioversion include those with:
- contraindications to anticoagulation
- structural heart disease (eg, large left atrium >5.5 cm, mitral stenosis) that precludes long-term maintenance of sinus rhythm
- a long duration of atrial fibrillation (usually >12 months)
- multiple failed attempts at cardioversion and/or relapses, even with concomitant use of antiarrhythmic drugs or non-pharmacological approaches
- an ongoing but reversible cause of atrial fibrillation (eg, thyrotoxicosis)

left to the treating doctor. Use of anticoagulation treatment may have had some effect on the outcome of the study, and in a subsequent retrospective analysis,[28] the use of anticoagulation treatment was an independent predictor of survival.

Although the AFFIRM investigators[29] reported a higher incidence of adverse pulmonary events associated with rhythm control, it was not stated whether this was due to the particular choice of rhythm control drug used rather than the strategy itself.

Also, the RACE, STAF, HOT CAFÉ and PIAF studies—which contributed approximately 25% to the total patient population—included patients with persistent atrial fibrillation, often with previous attempts at cardioversion and maintenance of sinus rhythm, and a fairly high risk of recurrence. In the AFFIRM study, 36% of patients were enrolled after the first episode of atrial fibrillation, many had paroxysmal atrial fibrillation and the duration of atrial fibrillation varied from several hours to several years. The differences in a qualifying episode of atrial fibrillation could account for a markedly higher incidence of long-term maintenance of sinus rhythm in the AFFIRM study (60% at 5 years) compared with RACE (40% at 3 years) and STAF (26% at 2 years). In the HOT CAFÉ study, 63.5% were in sinus rhythm at the end of the study, but the duration of follow-up was only 1 year. In the AFFIRM trial, 40% of the rate-control arm reverted spontaneously to sinus rhythm, and the closely similar primary endpoint results for the rhythm control and rate-control strategies may well be due to a general failure to achieve a clear difference with respect to rhythm and rate status in the two arms of the trials.

These data do not mean that rhythm control is not beneficial, but highlight the limitations of current treatments to achieve and maintain sinus rhythm. Poor efficacy, proarrhythmia and organ toxicity of antiarrhythmic drugs seem to negate the inherent advantage of sinus rhythm over atrial fibrillation.[28] Notably, there was a 1.5-fold excess of non-cardiovascular deaths, primarily due to pulmonary causes or cancer, in the rhythm-control arm of the AFFIRM study, but no difference in cardiovascular deaths.[29]

It is not uncommon for atrial fibrillation to coexist with congestive heart failure. Rate control has been advocated in patients with chronic congestive heart failure primarily owing to the notion that most antiarrhythmic drugs, except for amiodarone, are associated with increased mortality. However, it is unknown whether rhythm control may benefit patients with recent-onset, asymptomatic atrial fibrillation or those with mild left ventricular dysfunction. Retrospective analyses of large randomised controlled mortality studies have shown that sinus rhythm is a predictor of better survival in patients with New York Heart Association (NYHA) II–IV class heart failure irrespective of treatment assignment.[30 31] A retrospective analysis of >1000 patients with heart failure showed no difference in 2-year survival between patients in whom restoration and maintenance of sinus rhythm was attempted and those managed with rate control.[32] However, patients with heart failure were under-represented in the recent rate-control versus rhythm-control studies. For example, in the AFFIRM trial, 23% had a history of congestive heart failure and only 9% had a history of NYHA functional class ⩾II, and there was a non-significant trend towards better survival of these patients when assigned to rhythm control.[18] In the RACE study, approximately half the patients had a history of heart failure and NYHA functional class II,[19] and those treated with rate control had more hospitalisations for heart failure.[33] Conversely, patients treated with rhythm control had more thromboembolic events and were more likely to require a pacemaker. The ongoing Atrial Fibrillation and Congestive Heart Failure trial will examine whether the rhythm-control strategy reduces cardiovascular death in patients with NYHA class II—IV heart failure and an ejection fraction ⩽35%.[34]

Quality of life and cost efficacy

Quality of life analyses showed no major advantage of either a rate-control or a rhythm-control strategy probably because of the enrolment of less symptomatic patients, the inability to achieve stable sinus rhythm or adequate rate control in all patients, and the sizeable dropout and ''crossover'' rates.[24–27] All studies reported an overall improvement in quality of life with both treatment strategies. The AFFIRM and RACE studies also conducted formal economic analyses and found that rate control was generally more cost effective than rhythm control.[35 36] Higher costs associated with the primary rhythm-control strategy were driven by hospitalisations for cardioversion and initiation of antiarrhythmic drug treatment, pacemakers, emergency admissions, and outpatient visits to monitor the outcome and costs of antiarrhythmic drug prescriptions.

The health economic evidence from the National Institute for Health and Clinical Excellence guideline concluded that a rate-control strategy was more cost effective than a rhythm-control strategy. However, it was unclear whether the UK setting and outcome costs of inadequate anticoagulation would affect the results.

Therapeutic implications

The results of the rate versus rhythm trials generally pertain to patients with persistent atrial fibrillation, aged >65 years, who are mildly symptomatic, or to patients with persistent recurrent atrial fibrillation refractory to several drugs, but they cannot be

easily extrapolated to younger patients with paroxysmal or first-onset atrial fibrillation. Highly symptomatic patients, especially if they remain symptomatic despite rate control, must be considered for rhythm control. Because the outcome is very similar for both strategies, provided that anticoagulation continues to be used despite apparent resumption of sinus rhythm, doctors should discuss the pros and cons of both strategies with their patients and engage with the patient in making a decision. Non-pharmacological approaches to rhythm control should be considered when rate control is inappropriate (table 2).

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